of a) or b), each said change being a substitution, deletion or insertion of an amino acid, which analog binds to TRAF2 and modulates the activity of NF-κB; or

d) a derivative of a), b) or c) which binds to TRAF2 and modulates the activity of NF-κB.

53 (Amended). A polypeptide in accordance with claim 51, wherein said polypeptide of (a) is the polypeptide encoded by the nucleotide sequence of SEQ ID NO:6.

REMARKS

Claims 13-16, 20-22, 30, 43-60 and 62-68 presently appear in this case. No claims have been allowed. The official action of November 20, 2001, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to cDNA sequences which encode polypeptides that bind to TRAF2 and modulate activity of NF-κB, as well as the polypeptides encoded by those DNA sequences. Preferably, the polypeptide is NIK. The invention also relates to antibodies, methods of identification and screening, and antisense DNA.

The interview among Examiner Epps, Supervisory Examiner LeGuyader and the undersigned attorney on March 5, 2002, is hereby gratefully acknowledged. The enablement rejection of record was discussed and agreement was reached that the rejection under 35 U.S.C. §112 would be removed for claims 62 and 63. The examiners stated that the rejection of the remaining claims would

be reconsidered after applicants filed their written response. As the examiners now concede that at least claims 62 and 63 are allowable, it was requested that the present application be prepared for interference as per the request for interference under 37 C.F.R. §1.607, filed February 9, 2001.

Claims 51 and 53 have now been amended to correct minor clerical errors therein and, thus, place the case into better condition for allowance.

It is respectfully requested that the finality of the official action of November 20, 2001, be withdrawn. The grounds of the 35 U.S.C. §112, first paragraph, rejection in the official action of November 20, 2001, are completely different from the grounds of the rejection of May 8, 2001, and the change in grounds was not necessitated by any amendment of the claims by applicants (see MPEP §706.07(a)). In the May 8, 2001, rejection, the examiner states that the specification, while being enabling for polypeptides that inhibit or decrease the expression of NF-κB does not reasonably provide enablement for polypeptides which both inhibit and decrease the expression of NF-κB. In response to this ground of rejection, applicants amended the claims so that they no longer read on the possibility of peptides that both increase and decrease the expression of NF-κB. In view of the examiner's statement that the claims were enabling for polypeptides that inhibit or decrease the expression of NF-κB, and the claims were amended to be directed thereto, this ground of rejection was totally obviated. In response, the examiner made an entirely new rejection in the official action of November

20, 2001, stating that, while the claims are enabling for the nucleic acid molecules according to SEQ ID NOs:1, 4 and 6, they do not reasonably provide enablement for any other nucleic acid sequences encoding polypeptides which bind TRAF2 and either inhibit or decrease the expression of NF-κB. This ground of rejection had never been stated prior to final rejection. As this is effectively a new grounds of rejection, the official action November 20, 2001, should not have been final. Reconsideration and withdrawal of the finality of this rejection are respectfully urged.

Claims 13-16, 20-22, 30, 43-60 and 62-68 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the nucleic acid molecules according to SEQ ID NOs:1, 4 and 6, which encode polypeptides that bind TRAF2 and either inhibit or increase the expression of NF-κB, does not reasonably provide enablement for any other nucleic acid sequences encoding polypeptides that bind TRAF2 and either inhibit or increase the expression of NF-κB. The examiner states that there is no indication of what specific amino acid substitutions, deletions, insertions or amino acid modifications must be made to the polypeptides in order to isolate those polypeptides with the claimed activity. The examiner states that applicants have merely provided an invitation to experiment. This rejection is respectfully traversed.

First of all, as pointed out in the above-mentioned interview, claims 62 and 63 cover a peptide, and DNA encoding

such a peptide, having the amino acid sequence specifically set forth in SEQ ID NO:7, or an analog thereof that differs by the substitution, deletion or insertion of a single amino acid, which analog binds to TRAF2 and either inhibits or increases the activity of NF-κB. It would not involve undue experimentation to test substitutions, deletions or insertions of single amino acids within this defined sequence and test for binding to TRAF2 and then, for those polypeptides that bind to TRAF2, to test for modulation of the activity of NF-κB. In view of the functional language which states exactly what properties the analog must have and the fact that only one amino acid out of 947 is being changed, enablement in the specification is reasonable and any required experimentation would not be undue. Accordingly, in accordance with the agreement reached at the above-mentioned interview, reconsideration and withdrawal of this rejection, at least with respect to claims 62 and 63, are respectfully urged.

Claim 51, in part (a), is directed to polypeptides of a specified amino acid sequences. Part (c) includes analogs thereof having no more than ten changes in the amino acid sequence with each such change being a substitution, deletion or insertion of an amino acid. It further specifies that the analog must bind to TRAF2 and modulate the activity of NF-κB. It should be noted that the amino acid sequence of SEQ ID NO:2 is 604 residues, that encoded by the nucleotide sequence of SEQ ID NO:6 has 947 residues, and the amino acid sequence of SEQ ID NO:5 is 417 residues. Thus, ten changes in the 604 residue sequence

amounts to only 1.65%, i.e., 98.35% identity. Ten out 947 is 98.95% identity. Ten out of 417 is 97.61% identity.

The examiner's attention is invited to the Revised Interim Written Description Guidelines Training Materials, which have been published by the Patent and Trademark Office, Example 14 "Product by Function". There a claim to a specific sequence and variants thereof that are at least 95% identical thereto and have a specified function was held to comply with the written description requirement. The Guidelines state:

> The single species disclosed is representative of the genus because all members have at least 95% structural identity with the referenced compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

While these Training Materials relate to written description, rather than enablement, they should be instructive also from the standpoint of enablement to the extent that the Patent and Trademark Office has conceded that, with a claim such as the present, a single example is representative of the entire genus of variants with 95% identity. With the present claims, the identity is much greater than even 97%.

The test of enablement requires a determination of whether the disclosure contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The fact

that experimentation may be complex, does not necessarily make it undue if the art typically engages in such experimentation. See MPEP §2164.01. The factors to be considered in determining whether or not experimentation would be undue are the factors set forth in *In re Wands*, 8 USPQ2d 1400 (Fed Cir 1988), and include, but are not limited to:

A. the breadth of the claims;

B. the nature of the invention;

C. the state of the prior art;

D. the level of one of ordinary skill;

E. the level of predictability in the art;

F. the amount of direction provided by the inventor;

G. the existence of working examples; and

H. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the claims are not particularly broad, as the analogs require identity of greater than 97.5%, and in the claims that are limited to the NIK, the identity is nearly 99%. As indicated by the written description Training Materials, this is not considered to be undue breadth.

The nature of the invention is such that substantial experimentation is normally conducted by those of ordinary skill in the art. The level of skill in the art is quite high in biotechnology inventions. Furthermore, the function here requires two steps, binding to TRAF2 and testing for modulation of activity of NF-κB. The first binding step can be done using microarray technology that can test thousands of compounds at

once for binding. Only those that bind need then be further tested for modulation of activity. This is not undue experimentation in this art, particularly in view of the small number of amino acids that may be changed in accordance with the language of the claim.

As to the state of the prior art, it is clear that it is common for those of ordinary skill in the art to take part in this degree of experimentation as there are hundreds of patents that include claims with novel proteins and analogs of identity greater than 90%. This is not a case of first impression.

As to the predictability in the art, when changing the sequence by less than 2.5%, there would be an expectation that the function is maintained. Thus, it is reasonably predictable that such a small number of changes will work, but in any event, it is readily testable in order to determine which will have the claimed function and which will not have the claimed function. As to the amount of direction provided by the inventor, the specification discloses assays, discloses the types of substitutions which are considered conservative, and otherwise provides guidelines to assist in the experimentation necessary to make and use the invention. While there are no working examples relative to analogs, it is not necessary that every *Wands* factor be present, as long a overall the experimentation is not undue.

In light of this analysis and the relatively small deviation from identity permitted by the claims, the breadth of claim 51 allowing for ten amino acid changes should be acceptable for the same reasons that the examiners have already found

acceptable the variation of one amino acid change. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

As it has now been shown that all of the present claims are in condition for allowance and at least 62 and 63 have been conceded by the examiners as being in condition for allowance, it is urged that applicants' request for interference, as filed on February 9, 2001, be reconsidered and that steps be taken to declare an interference between the present application and U.S. patent 5,843,721 as soon as possible.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Version with Markings to Show Changes Made

Claims 51 and 53 have been amended as follows:

51 (Amended). A polypeptide that binds to TRAF2 and modulates the activity of NF-κB, said polypeptide comprising:

a) the amino acid sequence of SEQ ID NO:2, an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:6, or the amino acid sequence of SEQ ID NO:5;

b) an amino acid sequence of a fragment of a), which fragment binds to TRAF2 and modulates the activity of NF-κB;

c) an amino acid sequence of an analog of a) or b), having no more ~~that~~ than ten changes in the amino acid sequence of a) or b), each said change being a substitution, deletion or insertion of an amino acid, which analog binds to TRAF2 and modulates the activity of NF-κB; or

d) a derivative of a), b) or c) which binds to TRAF2 and modulates the activity of NF-κB.

53 (Amended). A polypeptide in accordance with claim 51, wherein said polypeptide of (a) is the polypeptide encoded by the nucleotide sequence of SEQ ID NO:6 ~~(NIK (SEQ ID NO:7))~~.